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ARMY ENVIRONMENTAL HYGIENE AGENCY ABERDEEN PROVING GR--ETC F/G 6/6
TOPICAL HAZARD EVALUATION OF CANDIDATE INSECT REPELLENT AI3-365--ETC(U)
MAY 77 M H WEEKS, B J DESENA

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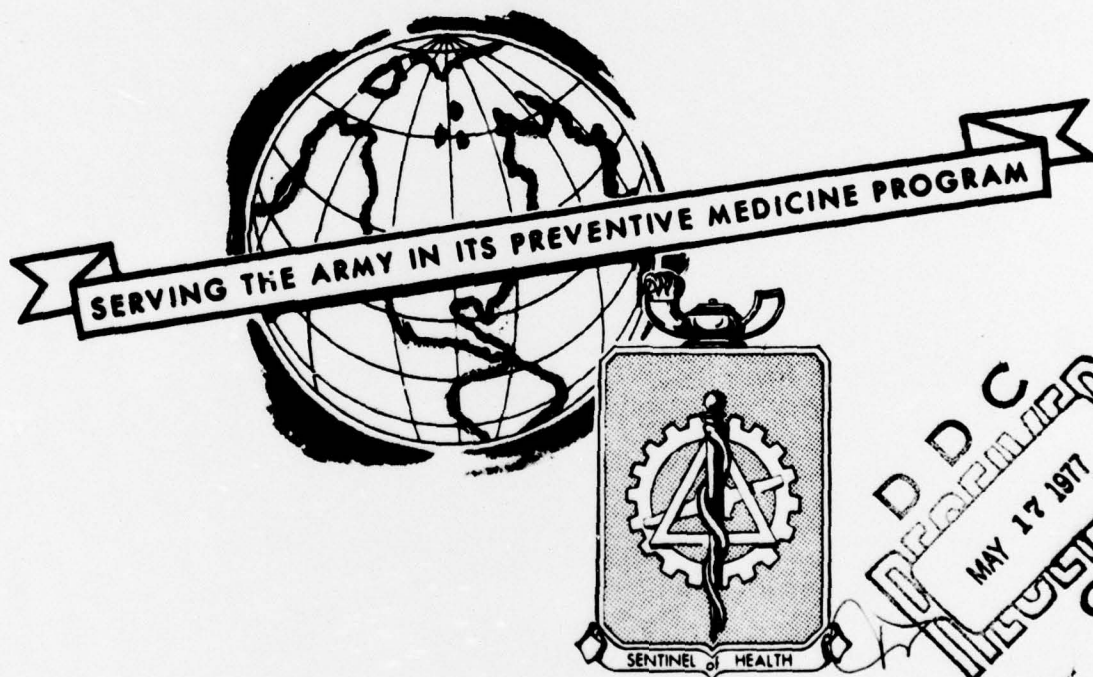


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TOPICAL HAZARD EVALUATION OF
CANDIDATE INSECT REPELLENT AI3-36558
3-METHYL-1-[(2-METHYLCYCLOHEXYL)CARBONYL]PIPERIDINE
TOPICAL HAZARD EVALUATION PROGRAM
STUDY NO. 51-0820-77
OCTOBER 1975 - DECEMBER 1976



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ABERDEEN PROVING GROUND, MD 21010

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) A hazard evaluation of AI3-36558 was conducted using New Zealand White rabbits for skin and eye studies, Hartley guinea pigs for a skin sensitization study, and Sprague-Dawley, Wistar-derived rats for determination of oral toxicity. It was found that AI3-36558 is a potential sensitizing chemical. Technical grade compound produced moderate injury to the cornea and to the conjunctiva of the rabbit and may cause similar damage if it should accidentally enter the eye of man. Based on these findings, it is recommended that AI3-36558 not be approved for further testing as a candidate insect repellent.		



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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

12 MAY 1977

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ABSTRACT

A hazard evaluation of AI3-36558 was conducted using New Zealand White rabbits for skin and eye studies, Hartley guinea pigs for a skin sensitization study, and Sprague-Dawley, Wistar-derived rats for determination of oral toxicity. It was found that AI3-36558 is a potential sensitizing chemical. Technical grade compound produced moderate injury to the cornea and to the conjunctiva of the rabbit and may cause similar damage if it should accidentally enter the eye of man. Based on these findings, it is recommended that AI3-36558 not be approved for further testing as a candidate insect repellent.

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1. AUTHORITY.

a. Letter, US Department of Agriculture, Agricultural Research Service, Southern Region, Insects Affecting Man Research Laboratory, Gainesville, FL, 17 October 1975.

b. Memorandum of Understanding Between the US Department of the Army, Office of The Surgeon General, the US Army Health Services Command, the US Army Environmental Hygiene Agency, the Armed Forces Pest Control Board and the US Department of Agriculture, effective December 1970 with Amendment No. 1, effective August 1974.

2. REFERENCE. Toxicology Division Procedural Guide, US Army Environmental Hygiene Agency (USAEHA), 1972.

3. PURPOSE. The purpose of this study was to provide guidance for further entomological testing of the candidate insect repellent AI3-36558.

4. SUMMARY OF FINDINGS. A hazard evaluation of the candidate repellent AI3-36558, 3-methyl-1-[(2-methylcyclohexyl)carbonyl]piperidine, was conducted by this Agency using New Zealand White rabbits for skin and eye studies, Hartley guinea pigs for a skin sensitization study, and Sprague-Dawley Wistar-derived rats for determination of oral toxicity. A tabular presentation of animal toxicity data developed in this Agency follows:*†

* In conducting the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," US Department of Health, Education, and Welfare Publication No. (NIH) 74-23, revised 1972, second printing 1974.

† The experiments reported herein were performed in animal facilities fully accredited by the American Association for Accreditation of Laboratory Animal Care.

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Study No. 51-0820-77, Oct 75-Dec 76

TABULAR PRESENTATION OF DATA

Test	Results	Interpretation
<u>SKIN IRRITATION STUDIES</u>		
<u>Rabbits</u>		
Single 24-hour application to intact and abraded skin of New Zealand White rabbits. 0.5 ml technical grade compound applied to each of six rabbits.	AI3-36558 produced mild irritation to the intact skin and to skin surrounding an abrasion.	USAEHA Category II (reference Appendix)
<u>EYE IRRITATION STUDIES</u>		
<u>Rabbits</u>		
Single 24-hour application of 0.1 ml of technical grade compound to one eye of each of six New Zealand White rabbits.	AI3-36558 produced moderate injury to the cornea and, in addition, some injury to the conjunctiva in six of six rabbits at 24 hr after application and for 3 days thereafter. No signs at seven days.	USAEHA Category E (reference Appendix)
<u>APPROXIMATE LETHAL DOSE (ALD)</u>		
<u>Oral</u>		
Rats (male) - no diluent	ALD = 3300 mg/kg Dosages of 430 mg/kg and higher caused nasal discharge.	Presents little lethal hazard from acute accidental ingestion.

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Test	Results	Interpretation
<u>PHOTOCHEMICAL SKIN IRRITATION STUDIES</u>		
<u>Rabbits</u>		
A single application (0.05 ml) of a 25-percent (w/v) solution of the compound (AI3-36558) and of a 10-percent (w/v) oil of Bergamot solution (positive control) in 95 percent ethyl alcohol, were applied to the intact skin of six rabbits. Five minutes after application, the rabbits were exposed to UV light (365 nm) for 30 minutes at a distance of 10-15 cm.	AI3-36558 did not cause a photochemical irritation reaction under test conditions.	Compound AI3-36558 did not cause a photochemical irritation reaction under test conditions and is not expected to cause a photochemical irritation reaction in humans.

CONTROL

Following UV exposure of the rabbits, 0.05 ml of the test compound, positive control and diluent were applied to additional skin areas to serve as unirradiated control sites. Application areas were checked for irritation at 24, 48 and 72 hours.	Positive control application and irradiation caused greater irritant effects than in unirradiated areas.
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SENSITIZATION STUDIES

Guinea Pig (male)

Intradermal injections of 0.1 ml of a 0.1 percent suspension (w/v) of AI3-36558 or dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.

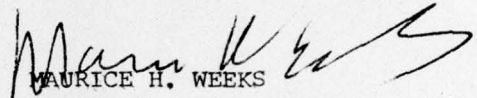
*A known skin sensitizer.

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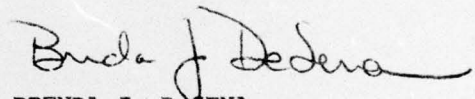
Test	Results	Interpretation
<u>SENSITIZATION STUDIES (cont)</u>		
<u>Guinea Pig (cont)</u>		
Ten test guinea pigs received and challenged with an 0.1 percent solution of AI3-36558	Challenge dose of test compound (last intradermal injection) produced a slight sensitization reaction in 2 out of 10 guinea pigs.	Compound AI3-36558 produced a slight sensitizing reaction under test conditions and may produce a sensitizing reaction in certain susceptible individuals.
Ten positive control guinea pigs received and challenged with 0.1 percent suspension of DNCB.	Positive control (DNCB) produced a marked sensitization reaction in 10 out of 10 guinea pigs.	
Ten cage control guinea pigs; five receiving challenge dose of test compound without prior sensitizing dose of DNCB without prior sensitizing dose.	Cage control guinea pigs showed no greater reaction to test compound and DNCB than were seen in original test groups.	

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5. CONCLUSION. AI3-36558 is a potential sensitizing chemical. Technical grade compound produced moderate injury to the cornea and to the conjunctiva of the rabbit and may cause similar damage if it should accidentally enter the eye of man.
6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (reference paragraph 1b), it is recommended that AI3-36558, 3-methyl-1-[(2-methylcyclohexyl)carbonyl]piperidine, not be approved for further testing as a candidate insect repellent.

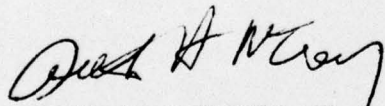


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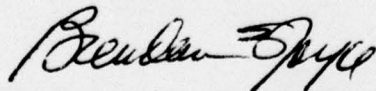


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APPENDIX

TOPICAL HAZARD EVALUATION PROGRAM
DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING
CONSIDERED FOR ACUTE SKIN APPLICATIONS

CATEGORY I - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

CATEGORY II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals, prior to human testing.

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion and, in addition, producing necrosis, vesiculation and/or eschars. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals, prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound. (INTERPRETATION: Not suitable for use on humans.)

EYE CATEGORIES:

A. Compounds noninjurious to the eye. INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.

B. Compounds producing mild injury to the cornea. INTERPRETATION: Should be used with caution around the eyes.

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C. Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. INTERPRETATION: Should be used with caution around the eyes and mucosa.

D. Compounds producing moderate injury to the cornea. INTERPRETATION: Should be used with extreme caution around the eyes.

E. Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva. INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.

F. Compounds producing severe injury to the cornea and to the conjunctiva. INTERPRETATION: Should be used with extreme caution. It is recommended that use be restricted to areas other than the face.